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Experimental Determination of the Activation Parameters and Stereoselectivities of the Intramolecular Diels–Alder Reactions of 1,3,8-Nonatriene, 1,3,9-Decatriene, and 1,3,10-Undecatriene and Transition State Modeling with the Monte Carlo-Jumping Between Wells/Molecular Dynamics Method

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Abstract: Experimental activation parameters for the intramolecular Diels–Alder reactions of 1,3,8-nonatriene, 1,3,9-decatriene, and 1,3,10-undecatriene have been measured, and the Monte Carlo-Jumping between Wells/Stochastic Dynamics [MC(JBW)/SD] method, which gives relative free energies of activation, was tested as a means to predict stereoselectivities. The predictions are compared to experimental results, and to predictions from quantum and molecular mechanics methods.

Introduction

The intramolecular Diels–Alder reaction is not only a fabulously successful reaction for synthesis, but has become the testing ground for computational methods which predict stereoselectivity. This paper reports the first quantitative measurements of the activation parameters for the intramolecular Diels–Alder reactions of three trienes which give 5-, 6-, and 7-membered rings fixed to cyclohexene upon cyclization. A new dynamics method that makes it possible to average over all accessible transition states has been tested for the first time for modeling organic stereoselectivity. By comparison to previous “one-state” models, the robustness of the new method has been demonstrated.

The new Monte Carlo-Jumping Between Wells/Stochastic Dynamics [MC(JBW)/SD] method¹ has been applied to the investigation of the intramolecular Diels–Alder (IDA)² reactions of 1,3,8-nonatriene (**1**), 1,3,9-decatriene (**2**), and 1,3,10-undecatriene (**3**) (Scheme 1). In the present study, this method was used to sample the accessible transition states of the reactions, and thus provided an extension of previous transition state modeling methods.³

New experimental measurements of ΔH^\ddagger and ΔS^\ddagger for the IDA reactions of **1–3** are also reported. In contrast to a previous study⁴ that measured only relative activation parameters for the *cis* and *trans* reaction pathways of **1** and **2**, activation parameters for each of the two pathways for the reactions of **1–3** are reported here.

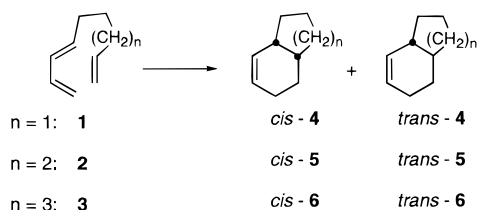
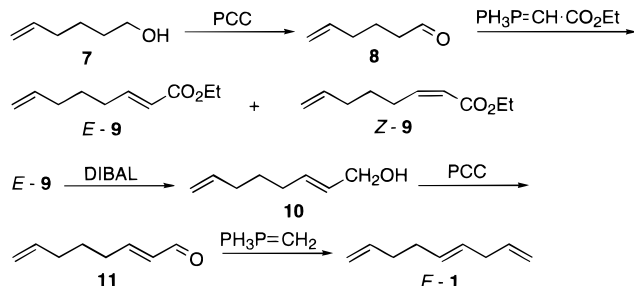
Subtle conformational effects⁵ which result in low to modest stereoselectivities make **1–3** stringent test systems for computational methods directed toward prediction of stereoselectivity,

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Scheme 1. IDA Reactions of 1,3,*n*-Trienes**Scheme 2.** Synthesis of (*E*)-Nonatriene (**1**)

and they have been used as test cases in several previous studies.^{3a,5,6} The stereoselectivities predicted by the MC(JBW)/SD calculations are compared to the new experimental results as well as to stereoselectivities predicted by previous *ab initio* and molecular mechanics methods.

Results and Discussion

Experimental Results. Most of the IDA reactions studied experimentally involve substituted systems. Only one experimental stereochemical study of IDA reactions of unsubstituted trienes has been reported. Lin and Houk determined relative activation parameters for the formation of the *cis* and *trans* fused unsaturated hydrindane (**4**) and decalin (**5**) systems from 1,3,8-nonatriene (**1**) and 1,3,9-decatriene (**2**, Scheme 1).⁴ Preferences of 1.0 and 0.3 kcal/mol for the formation of *cis-4* and *cis-5*, respectively, were found.

We have synthesized trienes (*E*)-**1**–**3**, and have measured the activation parameters for intramolecular Diels–Alder reactions of these structures to give both *cis* and *trans* adducts in the gas phase.

(*E*)-Nonatriene (**1**) was synthesized in five steps by a procedure adapted from Lin and Houk⁴ (**7**–**11**, Scheme 2). To avoid the tedious separation of isomers, an alternative route to prepare (*E*)-**2** and (*E*)-**3** was developed (Scheme 3). This approach utilized palladium-catalyzed coupling of alkynes with

vinyl halides as a key step.⁷ Mesylation of the alcohols **7** and **13** and subsequent reaction with lithium acetylide led to the alkynes **15** and **16** which underwent reaction with DIBAL in a highly specific *cis*-addition leading to (*E*)-vinylalanes **17** and **18**.⁸ The coupling of **17** and **18** with vinyl bromide in the presence of catalytic amounts of tetrakis(triphenylphosphine)-palladium(0) proceeded with retention of configuration⁹ affording the dienes (*E*)-**2** and (*E*)-**3**.

cis- and *trans*-bicyclo[5.4.0]undec-8-enes (*cis*- and *trans*-**6**), the products expected from the intramolecular Diels–Alder reaction of (*E*)-**3**, were independently prepared according to procedures reported by Christol, Mousseron, *et al.*¹⁰ and by McKenna *et al.*¹¹ (Scheme 4).

Upon gas-phase thermolysis at temperatures between 200 and 280 °C under carefully controlled conditions excluding acid catalysis, nonatriene (**1**) and decatriene (**2**) underwent clean IDA reactions leading to mixtures of *cis*- and *trans*-bicyclononene (**4**) and *cis*- and *trans*-bicyclodecene (**5**), respectively, which could be separated by preparative GC in each case. The corresponding rearrangement of undecatriene (**3**) required higher temperatures and proceeded with comparable rates of reaction only above 250 °C. In this case the bicyclic products *cis*- and *trans*-**6**¹² formed at 294 °C were assigned by GC comparison with authentic samples prepared by the procedure depicted in Scheme 4. The temperature dependence of the rates of formation of *cis* and *trans* cycloadducts was determined from the disappearance of trienes **1**, **2**, or **3**, and the *cis/trans* product ratios. Arrhenius parameters and ΔH^\ddagger and ΔS^\ddagger values for each system at 250 °C are given in Table 1.

The IDA reactions of trienes **1** and **2** have activation barriers close to that of the intermolecular Diels–Alder reaction of butadiene and ethylene,¹³ while the barrier for the reaction of **3** is a few kilocalories per mole higher. The primary effect of intramolecularity is to increase the ΔS^\ddagger by 11–14 eu relative to the reaction of butadiene with ethylene; this change in ΔS^\ddagger lowers ΔG^\ddagger by 6 to 9 kcal/mol.

At 250 °C, the IDA reaction of 1,3,8-nonatriene (**1**) is moderately *cis* stereoselective with a $\Delta\Delta G^\ddagger(\textit{cis}-\textit{trans})$ of -0.82 kcal/mol. This corresponds to a *cis:trans* product ratio of 69:31. Increasing the length of the methylene chain connecting the diene to the dienophile results in a decrease in *cis* stereoselectivity. The 1,3,9-decatriene (**2**) and 1,3,10-undecatriene (**3**) IDA reactions are essentially unselective, with *cis:trans* product ratios of 51:49 and 53:47, respectively. The results presented here are similar to those of Lin and Houk,⁴ who obtained *cis:trans* product ratios (252 °C) of 73:27 and 52:48 for the IDA reactions of **1** and **2**, respectively.

Theoretical Results. Several theoretical models including *ab initio*,^{3a,6} molecular mechanics,³ and combined *ab initio*/molecular mechanics calculations⁶ have been used to predict

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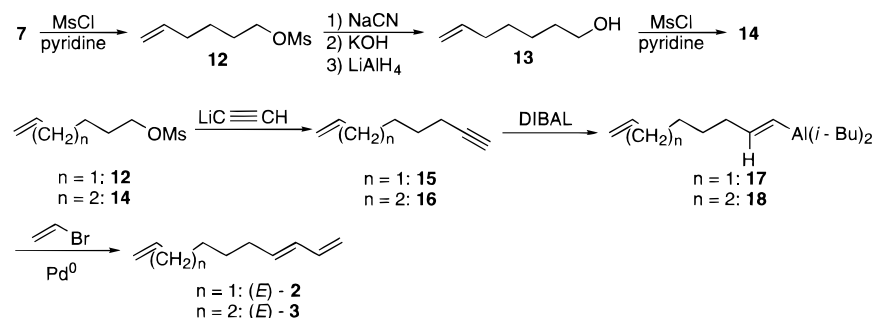
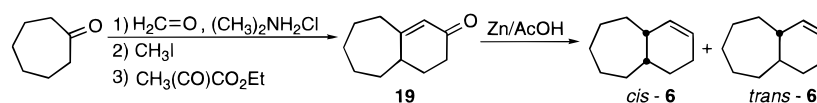
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Scheme 3. Synthesis of (*E*)-Decatriene (**2**) and (*E*)-Undecatriene (**3**)**Scheme 4.** Synthesis of *cis*- and *trans*-**6****Table 1.** Activation Parameters for the Intramolecular Diels–Alder Reactions of (*E*)-1,3,*n*-Trienes **1–3**^a

reaction	ΔE_a (kcal/mol)	log <i>A</i>	ΔH^\ddagger (kcal/mol)	ΔS^\ddagger (eu)
1 → <i>cis</i> - 4	26.32 ± 0.10	7.96 ± 0.04	25.28 ± 0.10	−25.21 ± 0.19
1 → <i>trans</i> - 4	27.79 ± 0.09	8.23 ± 0.04	26.75 ± 0.09	−23.97 ± 0.19
2 → <i>cis</i> - 5	25.41 ± 0.33	7.06 ± 0.14	24.37 ± 0.33	−29.32 ± 0.65
2 → <i>trans</i> - 5	25.56 ± 0.33	7.11 ± 0.15	24.52 ± 0.33	−29.10 ± 0.66
3 → <i>cis</i> - 6 ^b	30.95 ± 0.61	7.17 ± 0.23	29.91 ± 0.61	−28.82 ± 1.07
3 → <i>trans</i> - 6 ^b	31.01 ± 0.52	7.15 ± 0.20	29.97 ± 0.52	−28.91 ± 0.92

^a Enthalpies and entropies of activation given for reaction at 250 °C. ^b Extrapolated from an Arrhenius plot for the temperature range 267.2–325.5 °C.

Table 2. Relative Activation Parameters for the Intramolecular Diels–Alder Reactions of Trienes **1–3** at 250 °C

reaction	ΔH^\ddagger (<i>cis</i> – <i>trans</i>) (kcal/mol)	$\Delta\Delta S^\ddagger$ (<i>cis</i> – <i>trans</i>) (eu)	$\Delta\Delta G^\ddagger$ (<i>cis</i> – <i>trans</i>) (kcal/mol)	product ratio <i>cis</i> : <i>trans</i>
1 → 4	−1.47	−1.24	−0.82	69:31
2 → 5	−0.15	−0.22	−0.03	51:49
3 → 6	−0.06	0.09	−0.11	53:47

stereoselectivities of IDA reactions. All of these studies have utilized 1,3,8-nonatriene (**1**) and 1,3,9-decatriene (**2**, Scheme 1) as test systems. Using the MM2 force field,¹⁴ Lin and Houk determined that relative product stabilities could not account for the observed stereoselectivities in the IDA reactions of the unactivated trienes.⁴ On the basis of simple model calculations, Brown and Houk later attributed the *cis* selectivity in the reaction of **1** to unfavorable steric interactions and rationalized the low stereoselectivity of the IDA reaction of **2**.⁵ Raimondi and co-workers developed molecular mechanics transition state models for activated and unactivated Diels–Alder reactions based on *ab initio* transition structures of intermolecular Diels–Alder reactions,^{3a} and Brown and co-workers have studied the IDA reactions of 1,3,8-nonatriene (**1**) and 1,3,9-decatriene (**2**) using both *ab initio* methods and a hybrid *ab initio*/force-field approach that is implemented in the program QUEST.⁶ All of these previous models predicted stereoselectivities in good agreement with available experimental results.

We have studied the IDA reactions of **1–3** with transition state dynamics using the force field based Monte Carlo–Jumping Between Wells/Stochastic Dynamics method.¹ This approach has the advantage of including contributions of all conformationally distinct transition structures to the calculated relative free energy. The technique provides a solution to the problem

of sampling minima separated by substantial barriers. We used this method to calculate $\Delta\Delta G^\ddagger(\textit{cis}–\textit{trans})$ values for the IDA reactions of **1–3** for comparison with experimental results and with previous computational results.

Monte Carlo searches predict that each triene has multiple *cis* and *trans* transition structure conformations within 5 kcal/mol of the lowest energy one. Each corresponds to a minimum on its respective MM2*^{14,15} potential surface and is separated from the other minima by large energy barriers. Such PES features often result in slow convergence during standard molecular dynamics (MD) or stochastic dynamics (SD) simulations, since transitions between minima occur infrequently, or not at all.¹⁶ To address convergence difficulties of the type described above, Still and Guarnieri developed the hybrid MC/SD method which alternates between MC and SD steps during a simulation.¹⁷ The MC steps increase the probability of transition between conformational wells, while SD provides good sampling of each individual well. This method was found to converge several orders of magnitude more rapidly than SD for *n*-pentane.

The additional problem of small acceptance rates in Monte Carlo simulations, and consequently slow convergence, was later addressed by Senderowitz and co-workers. Their approach, termed Jumping Between Wells (JBW),¹ uses a conformational search to locate all low-energy conformers for a system. A series of transformations based on bond and dihedral angles which allows the interconversion of all pairs is then defined. The actual MC(JBW) simulation starts by determining which conformation the initial structure most closely resembles. The initial structure is then transformed to a new conformation which is randomly chosen from the conformer list. After random variations in the geometry of this new structure, its energy is compared to that of the initial structure, and it is then accepted or rejected based on the Metropolis criterion. This procedure results in a much higher step acceptance rate. The combination of this MC(JBW) method with the hybrid MC/SD technique of Guarnieri and Still results in a rapidly convergent dynamics technique that works efficiently for systems with conformations separated by large energy barriers.

This method holds considerable promise for the study of relative rates using transition state modeling techniques since

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Table 3. Relative Energetics of the *Cis* and *Trans* Pathways of the IDA Reactions of (*E*)-1,3,*n*-Trienes **1–3**^a

triene	exptl. ^b $\Delta\Delta H^\ddagger/\Delta\Delta G^\ddagger$	QM ^{b,c} $\Delta\Delta H^\ddagger/\Delta\Delta S^\ddagger/\Delta\Delta G^\ddagger$	MM ΔE^d	MC(JBW)/SD ^b $\Delta\Delta G^\ddagger$
1 → 4	-1.47/-0.82	-0.96/-0.74/-0.57	-1.20 (-0.83)	-0.96
2 → 5	-0.15/-0.03	0.05/-0.80/0.47	0.33 (0.25)	0.51
3 → 6	-0.06/-0.11	-0.12/0.68/-0.48	-0.04 (0.25)	0.57

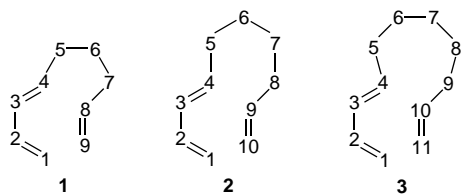
^a All differences are $E(\text{cis}) - E(\text{trans})$ and are in kcal/mol. Entropy differences are in eu. ^b Determined at 523 K. ^c RHF/3-21G with vibrational frequencies scaled by 0.8929. [Pople, J. A.; Schlegel, H. B.; Krishnan, R.; DeFrees, D. J.; Binkley, J. S.; Frisch, M. J.; Whiteside, R. A.; Hout, R. F. *Int. J. Quantum Chem. Symp.* **1981**, *15*, 269.] ^d ΔE values based on Boltzmann averages for all conformationally distinct transition structures for each triene are in parentheses.

it incorporates entropic effects. However, since transition state parameters are determined, in Houk's method,³ from the lowest energy transition state, there was no guarantee *a priori* that this method would be able to deal with conformational flexibility in transition states. This study was undertaken on a relatively well-understood system to determine how it behaved.

We explored the use of the MC(JBW)/SD method to calculate the $\Delta\Delta G^\ddagger(\text{cis-trans})$ (523 K) for the IDA reactions **1–3**. The Diels–Alder force field of Houk and Raimondi^{3a} was used in all cases. Relative free energies of activation were determined from:

$$G = -RT \ln K$$

where K is the *cis/trans* population ratio. This ratio was found by monitoring the H–C4–C8–H, H–C4–C9–H, and H–C4–C10–H torsional angles (*cis* $0 \pm 90^\circ$; *trans* $180 \pm 90^\circ$) in **1**, **2**, and **3**, respectively, during the simulations.

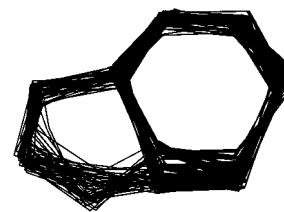


Monte Carlo conformational searches using the Diels–Alder force field were carried out first to determine all low-energy transition structures for each triene. Thus, the input for the MC(JBW)/SD simulations of **1**, **2**, and **3** included 5, 8, and 16 conformations, respectively.

All MC(JBW)/SD simulations were run for 10 ns with time steps of 0.5 fs at the experimental temperature of 523 K. To prevent isomerization of the double bonds and to maintain the *s-cis* conformation of the butadiene moieties, appropriate flat-bottom constraining potentials were used.

The $\Delta\Delta G^\ddagger(\text{cis-trans})$ values for each system are listed in Table 3. For the IDA reaction of **1**, the predicted $\Delta\Delta G^\ddagger(\text{cis-trans})$ is -0.96 kcal/mol, in excellent agreement with the experimental result of -0.82 kcal/mol. For this system, 10-ns simulations with either SD or MC/SD were also performed. Each simulation was initiated from a *cis* conformer, and no transitions to *trans* conformers were observed during either simulation. During the MC(JBW)/SD simulation, all conformationally distinct transition structures were sampled, and 2.6% of the interconversion attempts were successful (Figure 1). Thus MC(JBW)/SD samples the conformational spaces for these systems far more effectively than either SD or MC/SD. In fact, the MC(JBW)/SD simulations for each triene were essentially converged within 1 ns (Table 4).

Trans preferences of approximately 0.5 kcal/mol are predicted for **2** and **3**. Experimentally, the two reactions are practically unselective, with *cis* preferences of less than 0.2 kcal/mol.

**Figure 1.** Transition structures sampled during the first 500 ps (10-ps intervals) of the MC(JBW)/SD simulation of the Diels–Alder reaction of **1**.**Table 4.** $\Delta\Delta G^\ddagger(\text{cis-trans})$ Values for the IDA Reactions of **1–3** from MC(JBW)/SD Simulations^a

simulation time (ns)	1	2	3
1	-0.96	0.60	0.54
5	-0.96	0.50	0.54
10	-0.96 ± 0.04	0.51 ± 0.07	0.57 ± 0.05

^a Energies are in kcal/mol. Standard deviations were calculated by the method of block averages.

The largest deviation between experiment and prediction was less than 0.7 kcal/mol. A MC(JBW)/SD simulation of another test system, 3,9-dimethyl-1,3,9-decatriene, predicted a $\Delta\Delta G^\ddagger(\text{cis-trans})$ (463 K) of 2.4 ± 0.1 kcal/mol, in excellent agreement with the experimental result of 2.7 kcal/mol.¹⁸

For comparison, both *ab initio* and molecular mechanics methods were also used to predict the stereoselectivities of the IDA reactions of **1–3**. Monte Carlo conformational searches¹⁹ using the MM2* force field and the Diels–Alder transition state force field parameters of Raimondi et al.,^{3a} as implemented in the MacroModel/BatchMin 5.0 software package,¹⁵ were carried out to obtain all possible transition structures for the IDA reactions of trienes **1–3**. The Monte Carlo searches for **1**, **2**, and **3** were carried out for 10 000, 20 000, and 20 000 steps, respectively. For each system, all minima²⁰ found were within 5 kcal/mol of the lowest energy structure.

The differences in steric energies between the lowest energy *cis* and *trans* transition structures are given in Table 3. For the IDA reactions of **1** and **3**, the transition state models predict *cis* preferences of 1.20 and 0.04 kcal/mol, respectively, while a 0.33 kcal/mol *trans* preference is predicted for **2**. Boltzmann averaged energies over all conformers at the experimental temperature (523 K) give a *cis* preference of 0.83 kcal/mol for **1**, and predict slight *trans* preferences of 0.25 kcal/mol for both **2** and **3**.

The stereoselectivities predicted by MC(JBW)/SD are very similar to those predicted by either simple energy minimization or by Boltzmann averaged energies, the largest deviation between the methods being 0.6 and 0.3 kcal/mol, respectively. Transition structures for the concerted *cis* (endo) and *trans* (exo) pathways of the IDA reactions of **1–3** were also located with quantum mechanics at the RHF/3-21G²¹ level. Endo (**20**) and exo (**21**) transition structures for the reaction of **3** are shown in Figure 2. Geometries of the lowest energy endo and exo

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(20) While true transition states are defined as first order saddle points on potential energy surfaces, they are most often parametrized as minima with empirical force field models: see ref 3b. Two *cis* and three *trans* minima were found for nonatriene (**1**). Eight minima, four *cis* and four *trans*, were found for the decatriene (**2**) system. A total of 16 minima were located for undecatriene (**3**). Of these, eight corresponded to *cis*, and eight to *trans* transition structures.

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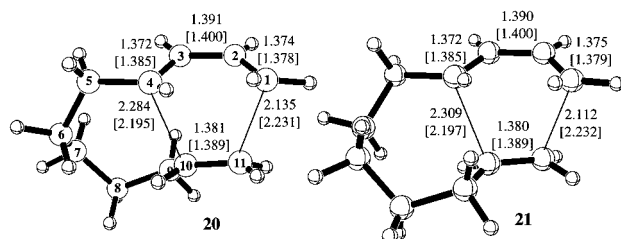


Figure 2. *Cis* and *trans* transition structures for the intramolecular Diels–Alder reaction of **3**. RHF/3-21G bond lengths are in plain text, and MM2* bond lengths are in square brackets. All bond lengths are in Å.

transition structures for each triene obtained from the Monte Carlo conformational searches were used as initial guesses for *ab initio* transition structure searches using Gaussian 94.²²

RHF/3-21G relative free energies (250 °C) for the IDA reactions of **1–3** are listed in Table 3. For **1** and **2**, the predicted $\Delta\Delta G^\ddagger$ values fall within 0.5 kcal/mol of the MC(JBW)/SD results, while the difference is larger (~ 1 kcal/mol) for **3**.

Conclusions

Activation parameters for the formation of *cis* and *trans* products in the intramolecular Diels–Alder reactions of nonatriene (**1**), decatriene (**2**), and undecatriene (**3**) have been determined. The activation enthalpies for the reactions of **1** and **2** are similar to that of the butadiene/ethylene intermolecular Diels–Alder reaction, while the barrier for **3** is a few kilocalories per mole higher. These IDA reactions are favored entropically by 11–17 eu over the parent Diels–Alder reaction. At 250 °C, the IDA reaction of **1** is moderately *cis* selective, forming a 69:31 ratio of *cis:trans* products. The IDA reactions of trienes **2** and **3** are essentially unselective, with only a few percent excess *cis* product formed in each case.

The stereoselectivity of each reaction was predicted by using transition state dynamics which gives $\Delta\Delta G^\ddagger(cis-trans)$ values including contributions from all low-energy *cis* and *trans* transition structures. The predicted $\Delta\Delta G^\ddagger(cis-trans)$ for the IDA reaction of **1** is within 0.2 kcal/mol of the experimental value. Experimentally, almost no stereoselectivity is observed for the decatriene (**2**) reaction, while MC(JBW)/SD predicted

slight *trans* stereoselectivity of about 0.5 kcal/mol. For **3**, a 0.6 kcal/mol preference for *trans* products is predicted. For this system, simple molecular mechanics provides the best agreement with experiment.

The transition state dynamics method performed well. It converged rapidly, and predicted $\Delta\Delta G^\ddagger(cis-trans)$ values within ± 0.7 kcal/mol of experimental values. In addition, it successfully sampled all conformationally distinct transition structures while both SD and MC/SD simulations failed to interconvert *cis* and *trans* transition structures. This technique should be particularly effective for systems with large entropy differences between transition structures or substantial differences in the shapes of their potential energy surfaces.

Experimental Section

Kinetic Measurements. Thermolyses of 1–3. Portions (250–300 mL each) of the solution of **1**, **2**, and **3**, respectively, and *n*-nonane, *n*-decane, and *n*-undecane as internal standards in *n*-hexane or *n*-heptane were injected into a thermostated and evacuated 20 l Pyrex flask. At each temperature the specific rate constants (Tables 1, 2, and 3, Supporting Information) were calculated from the time dependence of the disappearance of the triene versus the internal standard and the ratio of the forming bicyclic products by the use of the kinetic law for first-order irreversible reactions.

1. **1** (50 mg) and *n*-nonane (50 mg) in 5 mL of *n*-hexane: GC (column A, 50 °C); $t_R(n\text{-nonane}) = 6.1$ min, $t_R(\mathbf{1}) = 9.3$ min, $t_R(\text{trans-4}) = 12.1$ min, $t_R(\text{cis-4}) = 12.6$ min.

2. **2** (50 mg) and *n*-decane (50 mg) in 5 mL of *n*-heptane: GC (column A, 120 °C); $t_R(n\text{-decane}) = 4.4$ min, $t_R(\mathbf{2}) = 5.7$ min, $t_R(\text{trans-5}) = 8.5$ min, $t_R(\text{cis-5}) = 10.0$ min.

3. **3** (15 mg) and *n*-undecane (15 mg) in 5 mL of *n*-heptane: GC (column A, 120 °C); $t_R(n\text{-undecane}) = 5.1$ min, $t_R(\mathbf{3}) = 6.7$ min, $t_R(\text{trans-6}) = 13.2$ min, $t_R(\text{cis-6}) = 14.2$ min.

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Supporting Information Available: Experimental procedures, tables of kinetic data for the IDA reactions of **1–3**, and Cartesian coordinates for RHF/3-21G transition structures **20** and **21** (14 pages). See any current masthead page for ordering and Internet access instructions.

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