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Effect of a Methoxy Substituent on the Vinylcyclobutane Carbon Migration

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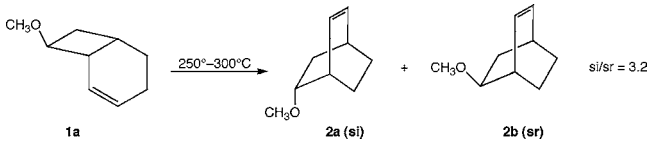

Over the temperature range 250−300 °C, 8-*exo*-methoxybicyclo[4.2.0]oct-2-ene (**1a**) undergoes a [1,3] sigmatropic rearrangement to 5-*exo*- and 5-*endo*-methoxybicyclo[2.2.2]oct-2-enes, **2a** and **2b**, respectively, with a clear preference for the *si* product: *si*/*sr* = 3.2. Both **1a** and its 8-*endo* epimer **1b** experience appreciable epimerization and fragmentation. A long-lived intermediate with weakly interacting diradical centers, one of which is stabilized by a methoxy substituent, can account for all such observations.

Introduction

Definitive elucidation of the mechanism of the vinylcyclopropane-to-cyclopentene rearrangement has been elusive; it has been viewed as exhibiting both stepwise and concerted characteristics. Studies related to the effect of a methoxy substituent on this [1,3] sigmatropic rearrangement have undoubtedly contributed to the debate. In 1973, Simpson and Richey reported that a methoxy label lowers the activation energy of the vinylcyclopropane-to-cyclopentene rearrangement by 5 kcal/mol when the methoxy substituent resides on C-1 in 1-methoxy-1-vinylcyclopropane and by 11 kcal/mol when the methoxy is at C-2 and of trans stereochemistry.[1] Although Simpson and Richey assumed that "an acyclic diradical intermediate is formed", others have challenged that assertion. In a comprehensive examination of a series of 1- and 2-substituted vinylcyclopropanes, de Meijere and Walsh have argued that the magnitude of the rate enhancement observed when the migrating carbon C-2 carries an alkoxy label is "inconsistent with biradical mechanisms".[2] Baldwin, in a recent review of the thermal rearrangements of vinylcyclopropanes to cyclopentenes, acknowledged that multiple interpretations have been accorded such substituent effects.[3] Fundamentally, our understanding of the effect of a methoxy substituent on the [1,3] sigmatropic rearrangement is far from complete.

Woodward and Hoffmann, in their treatise on the conservation of orbital symmetry, recognized that "a two step, non-concerted path for the conversion of vinylcyclopropane to cyclopentene is not thermodynamically unreasonable," given the substantial E_a of ca. 50 kcal/mol.[4] Citing earlier results consistent with this analysis, they posited the study of an appropriately labeled vinylcyclopropane to probe the "stereochemical consequences of the possible concerted processes" for this [1,3] sigmatropic rearrangement.[4] According to the Woodward−Hoffmann selection rules, a concerted reaction would afford the symmetry-allowed suprafacial inversion (*si*) and antarafacial retention (*ar*) products, not the symmetry-forbidden suprafacial retention (*sr*) and antarafacial inversion (*ai*) products. Through a series of elegant experiments, Baldwin has shown that vinylcyclopropanes judiciously labeled at the migrating carbon C-2 and the migration terminus instead access all four stereoisomeric products.[3]

Because the antarafacial topology is prohibitively strained in bicyclic vinylcyclopropanes, only the *si* and *sr* products can form without undue distortion of the carbon framework of the molecule. Consequently, the *si*/*sr* ratio has been viewed as a measure of the degree of orbital-symmetry control of the [1,3] carbon migration in both bicyclic vinylcyclopropanes and vinylcyclobutanes. Kirmse provided such an example with 8-*exo*-methoxybicyclo[5.1.0]oct-2-ene, which isomerized to 8-methoxybicyclo[5.1.0]oct-2-ene with an activation energy of 40.2 kcal/mol,[5a] a value close to the 38.7 kcal/mol reported by

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(3) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197−1212.

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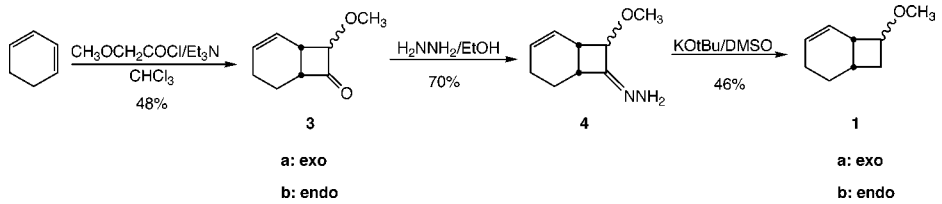
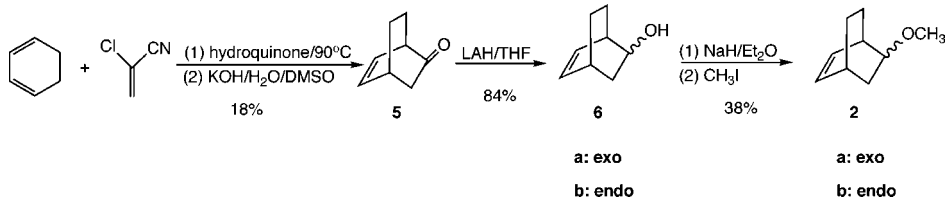
SCHEME 1. Synthesis of 8-Methoxybicyclo[4.2.0]oct-2-enes (1)



SCHEME 2. Synthesis of 5-Methoxybicyclo[2.2.2]oct-2-enes (2)



Richey for *trans*-2-methoxy-1-vinylcyclopropane.[1] This experimental investigation of the [5.1.0] system, moreover, provided unambiguous stereochemical results. When heated at ≥200 °C, 8-*exo*-methoxybicyclo[5.1.0]oct-2-ene gave exclusively the 8-*exo*-methoxy *si* product.[5b]

Bicyclo[2.1.1]hex-2-ene exists on the vinylcyclopropane thermal manifold because the thermal product bicyclo[3.1.0]-hex-2-ene, a bicyclic vinylcyclopropane, is more thermodynamically stable than the highly strained bicyclic vinylcyclobutane reactant. Scheidt and Kirmse in 1972 determined that 5-*anti*-methoxybicyclo[2.1.1]hex-2-ene undergoes a facile stereoselective [1,3] shift to 6-*exo*-methoxybicyclo[3.1.0]hex-2-ene, the *si* product, with E_a 10 kcal/mol lower[6] than that reported by Frey and Hopkins for the parent bicyclo[2.1.1]hex-2-ene.[7] The stereoselectivity (100% *si*) noted by Kirmse is particularly telling when examined against Frey's earlier statement in 1969 regarding the thermal study of bicyclo[2.1.1]hex-2-ene, the results of which "strongly support the concerted mechanism." Frey further argued this conclusion would be reinforced by the observation of inversion of stereochemistry at the migrating center in an "appropriately substituted derivative".[7a] While these results are entirely consistent with the characterization of a concerted reaction as energetically favorable and highly stereoselective,[8] the nature of vinylcyclobutane [1,3] sigmatropic rearrangements, concerted or stepwise, has not yet been resolved.[9]

Despite the obvious stereochemical and mechanistic parallels between vinylcyclopropane and vinylcyclobutane rearrangements noted by Baldwin in a recent review of vinylcyclopropane thermal chemistry,[3] the conspicuous absence of published thermal studies for other methoxy-labeled bicyclic vinylcyclobutanes has prompted the current study. We wish to report herein the results of thorough kinetic analyses of 8-*exo*-methoxybicyclo[4.2.0]oct-2-ene (**1a**) and 8-*endo*-methoxybicyclo-[4.2.0]oct-2-ene (**1b**). To provide meaningful comparisons between thermal studies of relevant bicyclo[3.2.0]hept-2-enes[10,11] and bicyclo[4.2.0]oct-2-enes,[12,13] this investigation will also focus on the stereochemical aspects of the [1,3] carbon shifts of **1a** and **1b** to **2a** and/or **2b**.

Results

Syntheses. The cycloaddition of 1,3-cyclohexadiene with methoxyketene, generated by treatment of methoxyacetyl chloride with triethylamine,[14] afforded a 48% yield of 8-methoxybicyclo-[4.2.0]oct-2-en-7-one (**3**) as an epimeric mixture in a 1:3 ratio of **3a**:**3b**, respectively. The two ketone epimers were separated via column chromatography to facilitate unambiguous structural elucidations. Differentiation between the endo and exo isomers was based on ^{1}H NMR chemical shifts, by analogy to Dreiding's structural assignments for the endo and exo epimers of 7-methoxybicyclo[3.2.0]hept-2-en-6-one,[14a] for which the C-7 hydrogen in the exo methoxy epimer is shielded relative to the corresponding hydrogen in the endo methoxy epimer. Similarly, the C-8 hydrogen is found at 4.3 ppm in **3a** as compared to 4.5 ppm in **3b**.

An epimeric mixture of **1a** and **1b** was prepared by subjecting compound **3** to a two-step cyclobutanone reduction sequence[15] based on low-temperature Wolff−Kishner reduction of the hydrazone derivative **4** (Scheme 1). As the epimers **1a** and **1b** have not previously been reported in the literature, they were separated and obtained in greater than 99% purity by preparative GC, and subjected to rigorous structural assignments by ^{1}H NMR and ^{13}C NMR spectroscopy. As with the ketone **3**, the most conspicuous difference in the ^{1}H NMR was the relative shielding of the C-8 hydrogen in the exo methoxy epimer: 3.6 ppm in **1a** versus 4.0 ppmin **1b**.

The synthesis of **2** (Scheme 2), as an epimeric mixture, originated with bicyclo[2.2.2]oct-5-en-2-one (**5**), a hydrolysis product derived from the Diels−Alder cycloadduct of 1,3-cyclohexadiene and 2-chloroacrylonitrile.[16] The cycloaddition, in the presence of hydroquinone, proceeded in fair yield, limited

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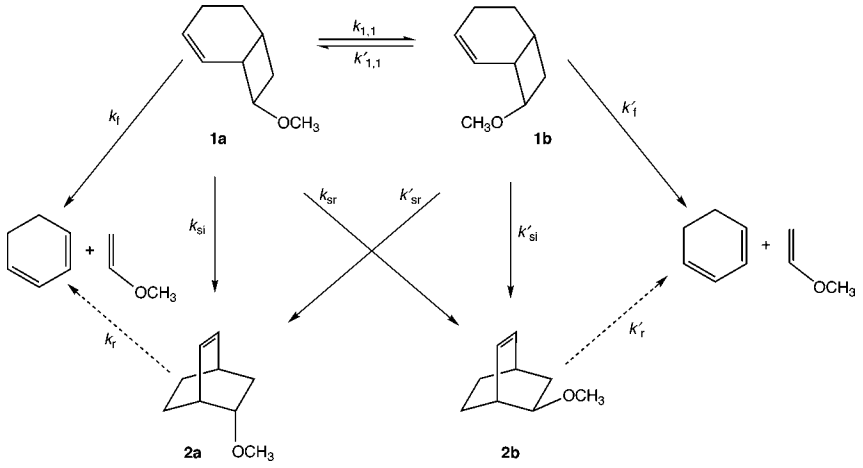
SCHEME 3. Kinetic Scheme

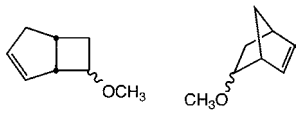


largely by the gradual evaporative loss of reactants during the course of the reaction. Because of the instability of the resultant cycloadduct, 5-chloro-5-cyanobicyclo[2.2.2]oct-2-ene was immediately hydrolyzed to compound **5**, a known stable crystalline solid with a characteristic melting point.[17] Spectral elucidation of **5** relied on ^{13}C NMR chemical shifts that closely match those reported in the literature[18−20] and an associated DEPT pulse sequence.

Reduction of **5** with LAH in THF proceeded in 84% yield and gave **6a** and **6b** in a 35:65 ratio as determined by integration of the corresponding C-2 hydrogens in the ^{1}H NMR spectrum run on the epimeric mixture, which crystallized as a white solid with a melting range of 160−163 °C. These distinctive NMR peaks at 3.83 and 3.93 ppm were selected because the chemical shift 3.97 ppm had previously been assigned to the H−COH signal in the endo alcohol **6b**.[21] The epimers were subsequently separated via column chromatography on Florisil to afford definitive spectra, ^{1}H NMR and ^{13}C NMR including DEPT, for each epimer. The NMR spectral data for the major epimer **6b**, which eluted second from the column, closely match those reported in the literature for the endo alcohol.[22,23]

Conversion of the alcohols to the methyl ethers was accomplished using standard Williamson ether synthesis conditions of sodium hydride followed by methyl iodide. Differentiation between the 5-*exo*- (**2a**) and 5-*endo*-methoxybicyclo[2.2.2]oct-2-ene (**2b**) epimers was based on ^{1}H and ^{13}C NMR characterization of each after preparative GC separation and purification. The first eluting compound, the minor epimer, gave ^{1}H and ^{13}C NMR spectra that closely matched those reported for **2a**.[24,25] Consistent with other examples of hydrogens residing in the shielding cone of a π-bond, the endo hydrogen at C-5 in **2a** is shielded by 0.2 ppm relative to the corresponding hydrogen in **2b**.

To make meaningful kinetic comparisons between the [3.2.0] and [4.2.0] analogues, 7-methoxybicyclo[3.2.0]hept-2-enes (**7**) and 5-methoxybicyclo[2.2.1]hept-2-enes (**8**) were also prepared. The ketone precursor of **7** is a known compound, the ketene cycloadduct of 1,3-cyclopentadiene and methoxyketene.[14] It was converted to **7** using the standard low-temperature Wolff−Kishner cyclobutanone reduction methodology.[15] Compound **8** is readily accessible from commercially available 5-norbornen-2-ol using Williamson ether synthesis conditions employed for the conversion of **6** to **2**.[26] The epimeric mixtures of **7** and **8** were easily separated via preparative GC and structurally characterized by NMR spectroscopy, in a manner analogous to that previously described for differentiation between the epimers of **1** andof **2**.



7 **8**

a: exo **a: exo**
b: endo **b: endo**

Thermolysis Reactions. Gas-phase thermal reactions of **1a**, **1b**, and a mixture of **2a** and **2b** were performed in a well-conditioned kinetic bulb[27] at 275.0 °C. Although compound **1a**, purified by preparative GC, contained less than 1% of **1b**, an impurity that was thermally stable at 275 °C was also present as a ca. 4% contaminant. This was ascertained by determining that the ratio of the amount of impurity that eluted at 15.3 min relative to the internal standard remained invariant at 0.0834 ± 0.0017 for 16 h. The most plausible identity of the impurity is 7-methoxybicyclo[4.2.0]octane based on its molecular ion peak at *m*/*z* 140. The formation of this unreactive impurity in all likelihood arose from the cycloaddition of methoxyketene with some cyclohexene present in commercial 1,3-cyclohexadiene.

Because of the enhanced reactivity of **1b**, which was obtained in greater than 99.5% by preparative GC, only short kinetic runs

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TABLE 1. Rate Constants ($\times 10^5$ s) Derived Using Simplified Parallel First-Order Reaction Model

compound	temp (°C)	k_d[a](k_d')[b]	$k_{1,1}$($k_{1,1}'$)	k_{si}(k_{si}')	k_{sr}(k_{sr}')	k_f(k_f')
1a	250	0.49 ± 0.03	0.24	0.11	0.04	0.10
	275	3.5 ± 0.2	1.6	0.9	0.3	0.7
	300	17.5 ± 0.7	3.9	5.1	1.7	6.8
1b	250	0.93 ± 0.04	0.46	0.02	0.1	0.35
	275	7.4 ± 0.2	4.1	N/A[c]	0.8	2.5
	300	34 ± 4	14	1	3	16

[a] Rate of overall disappearance of **1a**. [b] Rate of overall disappearance of **1b**. [c] Kinetic runs at shorter times resulted in only trace amounts of **2b**.

TABLE 2. Rate Constants ($\times 10^5$ s) Derived from Runge−Kutta Numerical Analysis

compound	temp (°C)	k_d(k_d')	$k_{1,1}$($k_{1,1}'$)	k_{si+sr}(k_{si+sr}')	k_f(k_f')
1a	250	0.55	0.3	0.15	0.1
	275	4.3	2.0	1.2	1.1
	300	22.5	8.0	8.0	6.5
1b	250	1.05	0.6	0.1	0.35
	275	8.3	5.0	0.5	2.8
	300	46.5	23.0	3.5	20.0

TABLE 3. Rate Constants for 7a, 7b, 8a, and 8b ($\times 10^5$ s)

cmpd	temp (°C)	k_d(k_d')	$k_{1,1}$($k_{1,1}'$)	k_{si}(k_{si}')	k_{sr}(k_{sr}')	k_f(k_f')	cmpd	temp (°C)	k_r[c](k_r')[d]
7a	275[a]	13.4	0.45	12.3	0.57	0.05	**8a**	275[a]	13
	272[b]	13.7	0.52	10.0	0.69			272[b]	10.6
7b	275[a]	4.4	0.54	0.07	1.8	2.1	**8b**	275[a]	51
	272[b]	3.7	0.54		1.6	1.6		272[b]	45.0

[a] This study. [b] Reference 30. [c] Rate of retro Diels−Alder reaction of **8a**. [d] Rate of retro Diels−Alder reaction of **8b**.

of 0.5, 1, 2, 3, and 4 h were performed over ca. 2 half-lives for **1b**. The thermal behaviors of **1a** and **1b** were also monitored at temperatures of 250 and 300 °C to determine Arrhenius parameters for comparisons with those reported for 8-*exo*-methylbicyclo[4.2.0]oct-2-ene[12] and bicyclo[4.2.0]oct-2-ene:[13b] for **1a**, $E_a = 42.6 \pm 1.3$ kcal/mol and $\log A = 12.5 \pm 0.5$; for **1b**, $E_a = 42.9 \pm 2.6$ kcal/mol and $\log A = 13 \pm 1$.

Because the thermal chemistry of **2a** and **2b** has not previously been explored, we heated a mixture of **2a** and **2b** containing undecane as an internal standard to show experimentally that the concentrations of **2a** and **2b** are relatively invariant up to 16 h at 275 °C, the longest thermal run for **1a** at this temperature. Not only was 99% of the mixture of **2a** and **2b** still present after 16 h, but the mole fraction of each did not change over this time interval: at $t = 0$ h, the **2a**:**2b** ratio was 0.491:0.509; at $t = 16$ h, it was 0.495:0.505.

The experimental first-order rate constants given in Table 1 correspond to thermal interconversions depicted in the kinetic scheme (Scheme 3). The rate data in Table 1 readily show that **1a** and **1b** interconvert by one-centered stereomutations at C8. In addition, **1a** undergoes both [1,3] sigmatropic rearrangements to **2a** and **2b** and fragments directly to 1,3-cyclohexadiene and methoxyethene, whereas **1b** experiences predominantly direct fragmentation with a relatively minor proportion of [1,3] shift rearrangements of mostly *sr* stereochemistry. All experimental first-order rate constants are given in Table 1 (*k* values refer to rate constants for **1a**; *k*′ values refer to those for **1b**).

Monitoring the disappearance of reactant **1a** or **1b** versus time provided rate constants for overall decompositions, k_d or k_d', respectively. Approximate experimental values for $k_{1,1}$ (or $k_{1,1}'$), k_{si} (or k_{si}'), k_{sr} (or k_{sr}'), and k_f (or k_f') were obtained from the slopes of linear plots of product mole fractions versus $(1 - e^{-k_d t})$; $k_{1,1}$ ($k_{1,1}'$) values, in particular, were obtained by graphical extrapolation to time zero. Because of the faster reaction rate at 300 °C, the experimental values for the rates of epimerization might well be too small.

The primary significance of a data reduction method is that the rate of epimerization can be treated explicitly. Thus, a Runge−Kutta four-step numerical integration[28] (calculated using an Excel spreadsheet) afforded modestly different rate constants, as reported in Table 2. The only meaningful difference was in the relative magnitude of k_d (k_d') at 300 °C; at this temperature, the Runge−Kutta rate constants in Table 2 are almost 30% larger than the experimental values in Table 1. At 300 °C, the experimental contributions from epimerization in both **1a** and **1b** are underestimated as compared to the corresponding Runge−Kutta rate constants in Table 2. Based on the Runge−Kutta rate constants in Table 2, there appears to be a general trend toward decreasing epimerization and increasing fragmentation with increasing temperature for both **1a** and **1b**.

A comprehensive thermal study of **7a** and **7b** has already been performed over the temperature range 248−284 °C.[29] A copy of Kampmann's Ph.D. thesis, while unpublished, was generously made available to us in electronic format by a librarian at Ruhr University (formerly University of Bochum).[30] We have independently conducted a kinetic analysis of **7a** and **7b** at 275 °C to corroborate Kampmann's kinetic results in our pyrolysis apparatus. Although not identical, the rate constants obtained in both investigations at 275 °C in our laboratory, and at 272 °C in Kirmse's laboratory, are in reasonably good agreement (Table 3).

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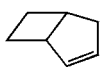
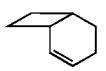
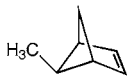
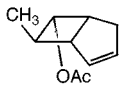
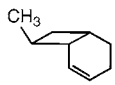
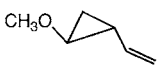
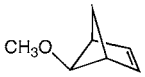
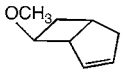
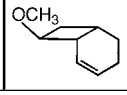
TABLE 4. Activation Parameters for Vinylcyclopropanes and a Series of Bicyclic Vinylcyclobutanes[a]

Compound	E_a*	log A	Compound	E_a*	log A	Compound	E_a*	log A	Compound	E_a*	log A
	51.7[3] 49.7[38]	14.3 13.6		35.2[7]	14.0		48.6[39]	14.8		51.8[13b]	14.9
	48.7[2]	13.7		—	—		47.1[40]	14.2		44.3[12]	12.8
	38.7[1]	12.5		25.1[6]	13.3		46.3[29,30]	14.7		42.6	12.5

[a] "*" represents units of kcal/mol.

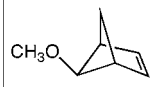
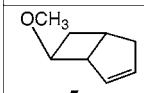
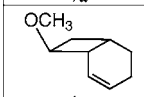
Discussion and Conclusions

The impetus for this study has been to test the generality of methoxy-promoted rate enhancements in vinylcyclobutane-to-cyclohexene rearrangements. Given the apparent universality of [1,3] rate acceleration of the vinylcyclopropane-to-cyclopentene rearrangement and other related reactions due to a methoxy-labeled migrating carbon, Kirmse had stated categorically that "the rates of 1,3-carbon shifts are strongly accelerated by alkoxy substitution at the migrating carbon; activation energies are lowered by 40−63 kJ mol^{-1} compared to the corresponding rearrangements of the parent hydrocarbons."[31] He further expounded that "these effects have been explained in terms of the stabilization that alkoxy substituents afford to free radicals, although some of the reactions studied may proceed by concerted paths."[31] The validity of this assertion rests on an examination of the magnitude of the radical-stabilizing effect of alkoxy groups.

Because of the difficulty in obtaining accurate experimental values of radical stabilization energies, theoretical values have been utilized instead. Radical stabilization energies calculated, according to an isodesmic reaction, for methoxy and methyl substituents are 5.30 and 3.27 kcal/mol, respectively.[32] Given E_a values of 42.6, 44.3, and 51.8 kcal/mol for thermal reaction of **1a**, 8-*exo*-methylbicyclo[4.2.0]oct-2-ene,[12] and bicyclo[4.2.0]-oct-2-ene,[13b] respectively, our results are in qualitative agreement with these radical-stabilizing substituent effects and consistent with the trends observed for both the vinylcyclopropane-to-cyclopentene and the bicyclo[2.1.1]hex-2-ene-to-bicyclo[3.1.0]-hex-2-ene rearrangements (Table 4). The observed order of decreasing reactivity (CH_3O > CH_3 > H) corresponds to the order of decreasing electron-donating ability. Based on a density functional theory (DFT) computational study of vinylcyclopropane−cyclopentene rearrangements, Houk and co-workers have surmised that the relative order of radical stabilization when the migrating carbon carries a substituent group parallels the polarizability of the substituent.[33]

Relatively few computational studies have been directed toward explicating the apparent rate-accelerating effect of electron-donating substituents on [1,3] carbon shifts. Sperling and Fabian have recently examined substituent effects on the vinylcyclopropane−cyclopentene rearrangement using DFT. The authors assert that their findings are in agreement with earlier conclusions that the "substituent effects on the activation energies are closely connected with the radical stabilizing properties of the substituents."[34] Using a hydroxy group as a model of a donor substituent, Sperling and Fabian have determined that a hydroxy substituent on the migrating carbon in vinylcyclopropane stabilizes both the reactant (by 7.8 kcal/mol) and the [1,3] transition state (by 16.9 kcal/mol). The difference of 9.1 kcal/mol, a value close to the 11 kcal/mol observed earlier by Simpson and Richey[1] for *trans*-2-methoxy-1-vinylcyclopropane versus 1-vinylcyclopropane, represents a net stabilization of the E_a of the vinylcyclopropane-to-cyclopentene rearrangement. The authors believe that, to a good approximation, this large substituent effect in the transition state model is in accord with two weakly interacting radical centers.[34]

TABLE 5. Stereochemistry of [1,3] Carbon Shifts in Methoxy-Labeled Bicyclic Vinylcyclobutanes

	si (%)	*sr* (%)	*si*/*sr*	*sr*/*si*	ref.
	>99	<1	100	0	6
 **7a**	95.5 93.5	4.5 6.5	21 14	0.05 0.07	this work 30
 **1a**	76	24	3.2	0.32	this work

The most compelling evidence for a biradical intermediate in [1,3] carbon shifts is the formation of all possible product stereoisomers, although not in equal proportion, consistent with dynamic control of the reaction.[3,9] Because bicyclic vinylcyclopropanes and vinylcyclobutanes can only access two of the four possible stereoisomeric products, the *si*/*sr* is an extremely sensitive probe of the rotational propensity of the migrating carbon and, as a corollary, the lifetime of the resultant biradical intermediate. The tabulated stereoisomeric results for a series of methoxy-labeled bicyclic vinylcyclobutanes (Table 5) reveal that the strong preference for the symmetry-allowed *si* product decreases as a function of the overall conformational flexibility

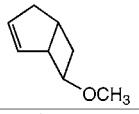
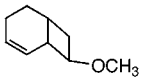
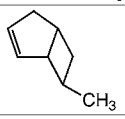
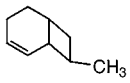
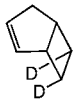
(31) Kirmse, W.; Zeppenfeld, M. *J. Chem. Soc., Chem. Commun.* **1977**, 124.

(32) Pasto, D. J.; Krasnansky, R.; Zercher, C. *J. Org. Chem.* **1987**, *52*, 3062−3072.

(33) Nendel, M.; Sperling, D.; Wiest, O.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 3259−3268.

(34) Sperling, D.; Fabian, J. *Eur. J. Org. Chem.* **1999**, 215−220.

TABLE 6. Stereochemical [1,3] Ratio (*si*/*sr*) and Rate Ratio of [1,3] Shift to Fragmentation ($k_{1,3}/k_f$) at 275 °C for Bicyclo[3.2.0]hept-2-enes and Bicyclo[4.2.0]oct-2-enes

Compound	si/sr	$k_{1,3}/k_f$	Ref.	Compound	si/sr	$k_{1,3}/k_f$	Ref.
	21	260	this work		3.2	1.1	this work
	7	130	11		2.4	0.3	12
	3	2.1	10		1.4	0.44	13

of the reactant. In reporting almost complete stereoselectivity for 5-*anti*-methoxybicyclo[2.1.1]hex-2-ene (first entry in Table 5), Scheidt and Kirmse initially attributed the stereochemical result to a concerted reaction.[6] Reconsideration of these results in comparison to less strained variants of bicyclic vinylcyclobutanes, however, reveals an incremental decrease in the *si* product corresponding to a decrease in the total geometric constraint of the ring in which the vinyl group resides. For 8-substituted bicyclo[4.2.0]oct-2-enes, a methoxy (76% *si*, 24% *sr*) as compared to a methyl (71% *si*, 29% *sr*) substituent on the migrating carbon affords a negligible stereochemical difference: *si*/*sr* = 3.2 for methoxy versus 2.4 for methyl (Table 6).

Although it is tempting to attribute the apparent increase in stereoselectivity due to a methyl or methoxy (relative to the unlabeled parent hydrocarbon) to the steric effect of the substituent, the critical difference is probably a function of the mass rather than the size of the substituent. Angular momentum, which appears to dominate rotational torque in diradical intermediates, depends on mass. The heavier is the substituent on the migrating carbon, the slower is the bond rotation.[35] Stereoselectivity, as determined by the *si*/*sr* ratio, decreases in the following order as the rate of bond rotation increases: CH_3O > CH_3 > D (Table 6).

Based on activation energy trends in Table 4, the bicyclo[3.2.0]hept-2-enes appear atypical. That bicyclo[3.2.0]hept-2-enes have yielded anomalous results as compared to other vinylcyclobutanes is further corroborated by the data in Table 6, where the $k_{1,3}/k_f$ ratio might represent a qualitative measure of the inward migratory aptitude of the migrating carbon. The exceedingly large $k_{1,3}/k_f$ ratios for the 7-*exo*-methyl- and 7-*exo*-methoxybicyclo[3.2.0]hept-2-enes suggest that methyl and methoxy substituents on the migrating carbon C-7 strongly favor inward migration, yielding correspondingly larger proportions of the [1,3] product relative to fragments. Alternatively, this phenomenon might be attributed to dynamic factors that could well be unique to bicyclo[3.2.0]hept-2-enes such as maximal orbital interaction between the migrating carbon C7 and C1 during bond cleavage.[35] According to the Sperling−Fabian paradigm,[34] it is possible that bicyclo[3.2.0]hept-2-enes, unlike the other vinylcyclobutanes and vinylcyclopropanes, generate intermediates with two less weakly, or more strongly, interacting radical centers. Such a diradical would account for the smaller ΔE_a values (Table 4) and larger *si*/*sr* ratios (Table 6) observed for the bicyclo[3.2.0]hept-2-enes.

(35) Carpenter, B. K. *J. Am. Chem. Soc.* **1995**, *117*, 6336−6344.

If this mechanistic model were valid, then the bicyclo[4.2.0]-oct-2-enes, like the vinylcyclopropanes, might undergo bond homolysis to afford intermediates with weakly interacting radical centers. Enhanced bond rotation with consequent reduced stereoselectivity, as is seen experimentally, would be anticipated for a diradical intermediate with these characteristics. In such cases, radical-stabilizing substituents such as methyl and methoxy should effect maximum rate acceleration (Table 4). This is an obvious instance where computational efforts might well provide great insight.

Experimental Section

8-Methoxybicyclo[4.2.0]oct-2-en-7-one (3). To a solution of 50 mL of 1,3-cyclohexadiene (42 g, 0.52 mol) and 17 mL of methoxyacetyl chloride (20 g, 0.18 mol) in ca. 100 mL of chloroform was added a solution of 26 mL of triethylamine (19 g, 0.19 mol) in 20 mL of chloroform dropwise over ca. 8 h. The reaction mixture was then stirred overnight at room temperature. After removal of the chloroform via simple distillation and the triethylamine hydrochloride by vacuum filtration, the salt was washed with ether. The filtrate was washed successively with water and brine and dried over $MgSO_4$. Vacuum distillation afforded 13.5 g (48%) of compound **3**, an isomeric mixture of endo:exo epimers in an 81:19 ratio by GC; it was isolated as a viscous oil. IR (cm^{-1}) 3010 (w), 1770 (s), 690 (m); MS (*m*/*z*) 152 (M, 11%), 124 (40%), 109 (23%), 97 (100%), 92 (83%), 79 (90%), 77 (45%). The exo and endo epimers were separated using column chromatography by elution with 95:5 pentane:ether from silica gel. 8-*exo*-Methoxybicyclo[4.2.0]oct-2-en-7-one (**3a**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (m, 1H), 5.94 (m, 1H), 4.29 (dd, 1H), 3.45 (s, 3H), 3.25 (m, 1H), 2.72 (b m, 1H), 1.95 (m, 2H), 1.83 (m, 1H), 1.63 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6 (C═O), 129.5 (HC═), 126.1 (HC═), 95.2 (HCO), 57.9 (H_3CO), 51.2 (HC), 32.3 (HC), 21.5 (H_2C), 20.5 (H_2C). 8-*endo*-Methoxybicyclo[4.2.0]oct-2-en-7-one (**3b**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (m, 1H), 5.79 (m, 1H), 4.54 (dd, 1H), 3.48 (s, 3H), 3.38 (m, 1H), 3.19 (m, 1H), 2.03 (m, 3H), 1.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9 (C═O), 130.9 (HC═), 122.4 (HC═), 88.3 (HCO), 58.7 (H_3-CO), 48.9 (HC), 29.6 (HC), 20.9 (H_2C), 17.1 (H_2C).

8-Methoxybicyclo[4.2.0]oct-2-en-7-one Hydrazone (4). To a solution of 5.0 mL (0.16 mol) of anhydrous hydrazine in 25 mL of absolute ethanol was added 4.2 g (0.028 mol) of compound **3** dissolved in 5 mL of absolute ethanol. After the reaction mixture was heated overnight at 60 °C, the reaction was quenched with 40 mL of water and extracted five times with methylene chloride. The organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Bulb-to-bulb distillation gave **4** (3.23 g, 70%). IR (cm^{-1}) 3375 and 3270 (w, NH_2), 3020 (w), 1630 (w,

C═N), 700 (s); MS (*m*/*z*) 166 (M, 21%), 151 (28%), 138 (37%), 123 (100%), 106 (40%), 91 (40%), 79 (94%), 77 (68%), 70 (72%), 60 (67%).

8-Methoxybicyclo[4.2.0]oct-2-ene (1). To a solution of 3.37 g (30.0 mmol) of potassium *tert*-butoxide in 25 mL of anhydrous DMSO was added 3.23 g (19.4 mmol) of **4** via syringe over 5−6 h. The reaction mixture was stirred overnight and then quenched with water and extracted with pentane. The organic extract was washed seven times with water, dried over $MgSO_4$, filtered, and concentrated by simple distillation. The crude product (1.22 g, 46%) consisted of a 26:74 (as determined by GC) mixture of **1a**:**1b**, respectively. IR (cm^{-1}) 3015 (w), 1120 (s), 730 (s); MS (*m*/*z*) 138 (M, 100%), 109 (31%), 96 (83%), 95 (43%), 82 (56%), 81 (81%), 67 (74%). Separation of the epimers was achieved via preparative GC. 8-*exo*-Methoxybicyclo[4.2.0]oct-2-ene (**1a**): ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (dd, 2H), 3.61 (dd, 1H), 3.24 (s, 3H), 2.59 (br s, 1H), 2.36 (m, 1H), 1.95 (m, 4H), 1.75 (m, 1H), 1.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.9 (HC═), 128.0 (HC═), 81.7 (HCO), 55.8 (H_3CO), 41.2 (HC), 31.4 (H_2C), 26.7 (H_2C), 25.6 (HC), 22.6 (H_2C). 8-*endo*-Methoxybicyclo[4.2.0]oct-2-ene (**1b**): ^1H NMR (500 MHz, $CDCl_3$) δ 5.98 (br m, 1H), 5.72 (br d, 1H), 3.95 (dd, 1H), 3.24 (s, 3H), 2.94 (br s, 1H), 2.19 (br m, 1H), 2.14 (m, 1H), 2.07 (m, 2H), 1.73 (dd, 1H), 1.54 (m, 1H), 1.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.3 (HC═), 124.5 (HC═), 76.8 (HCO), 56.1 (H_3CO), 38.5 (HC), 30.0 (H_2C), 24.1 (HC), 21.1 (H_2C), 21.0 (H_2C).

Bicyclo[2.2.2]oct-5-en-2-one (5). To a solution of 27 mg of hydroquinone in 20 mL (0.18 mol) of 1,3-cyclohexadiene was added 10 mL (11 g, 0.12 mol) of 2-chloroacrylonitrile (pretreated with potassium hydroxide pellets from which it was decanted before addition). The reaction mixture was heated at reflux overnight in the dark at 90 °C, an additional 10 mL of 1,3-cyclohexadiene was added, and the reaction mixture was again heated at reflux overnight. The brown reaction mixture was diluted with 15 mL of CH_2Cl_2, and the resultant solution was filtered through a short silica gel column and concentrated under reduced pressure to yield 6.9 g of a dark brown liquid. IR (cm^{-1}) 3040 (w), 2240 (w), 1650 (w), 710 (s).

To a solution of the viscous residue in 95 mL of DMSO was slowly added an aqueous solution of 11.6 g of KOH in 20 mL of water over 4 h with continuous stirring. Stirring was continued for an additional 20 h; 200 mL of water was added, and the aqueous solution was extracted five times with pentane. The organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 2.6 g (0.021 mol, 18% overall) of **5** as a white crystalline solid (mp 85−88 °C). IR (cm^{-1}) 3040 (w), 1725 (s), 1610 (w), 700 (s); MS (*m*/*z*) 122 (23%), 80 (100%), 79 (88%), 39 (17%); ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (t, 1H), 6.17 (t, 1H), 3.10 (br t, 1H), 2.96 (m, 1H), 2.00 (m, 1H), 2.00 (m, 1H), 1.83 (m, 1H), 1.67 (m, 2H), 1.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.2 (C═O), 137.0 (HC═), 128.4 (HC═), 48.5 (HC), 40.5 (H_2C), 32.3 (HC), 24.2 (H_2C), 22.5 (H_2C).

Bicyclo[2.2.2]oct-5-en-2-ol (6). To a solution of 0.38 g (3.1 mmol) of **5** in 25 mL of anhydrous THF at 0 °C was added 6.0 mL of 1.0 M $LiAlH_4$ in THF slowly via syringe. After the addition was complete, the reaction was allowed to warm to rt and stirred for 4 h. It was then cooled to 0 °C and quenched with cold ethanol. The reaction mixture was treated sequentially with satd NH_4Cl, ether, 1 N HCl, and water. After separation of the ether layer, the aqueous layer was extracted four more times with ether. The combined organic extracts were then washed with satd $NaHCO_3$, 1 N HCl, water, and brine, dried over $MgSO_4$, filtered, and concentrated at reduced pressure to yield **6** (0.32 g, 84%) as a white solid (mp 159−163 °C). IR (cm^{-1}) 3310 (m), 3040 (w), 1725 (s), 1615 (w), 710 (s). Flash chromatography from Florisil using 95:5 pentane:ether separated the epimers; the exo alcohol was the first eluting component.[36] *exo*-Bicyclo[2.2.2]oct-5-en-2-ol (**6a**): ^1H NMR (500 MHz, $CDCl_3$) δ 6.26 (t, 1H), 6.18 (t, 1H), 3.83 (br d, 1H), 2.51 (br m, 2H), 2.04 (m, 1H), 1.83 (m, 1H), 1.64 (m, 1H), 1.43 (s, 1H), 1.27 (m, 1H), 1.13 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4 (HC═), 131.9 (HC═), 69.4 (HCO), 37.7 (HC), 35.7 (H_2C), 30.0 (HC), 25.9 (H_2C), 17.2 (H_2C). *endo*-Bicyclo[2.2.2]-oct-5-en-2-ol (**6b**): ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (t, 1H), 6.12 (t, 1H), 3.93 (br m, 1H), 2.73 (br m, 1H), 2.58 (br m, 1H), 1.98 (ddd, 1H), 1.64 (s, 1H), 1.34 (m, 3H), 1.12 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9 (HC═), 129.7 (HC═), 70.5 (HCO), 39.2 (H_2C), 37.8 (HC), 30.1 (HC), 24.0 (H_2C), 21.8 (H_2C).

5-Methoxybicyclo[2.2.2]oct-2-ene (2). To a suspension of 132 mg (5.5 mmol) of sodium hydride (220 mg of a 60% dispersion in mineral oil, which was removed by rinsing with pentane) in 10 mL of anhydrous THF was added dropwise a solution of 0.30 g (2.4 mmol) of **6** in 20 mL of THF. After 2 h, 1.5 mL (3.4 g, 24 mmol) of methyl iodide was added to the reaction mixture, which was then stirred overnight. The reaction mixture was quenched with enough methanol to dissolve the solid and then diluted with 100 mL of ether. The organic material was washed four times with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude **2** (0.13 g, 38%), a 29:71 mixture of **2a**:**2b**, respectively, as determined by GC analysis. IR (cm^{-1}) 3040 (w), 1620 (w), 1100 (s), 710 (s); MS (*m*/*z*) 138 (M, 100%), 123 (82%), 91 (79%), 79 (40%). Epimeric separation was achieved via preparative GC. 5-*exo*-Methoxybicyclo[2.2.2]oct-2-ene (**2a**): ^1H NMR (500 MHz, $CDCl_3$) δ 6.27 (t, 1H), 6.13 (t, 1H), 3.28 (s, 3H), 3.29−3.27 (m, 1H), 2.74 (br m, 1H), 2.46 (br m, 1H), 1.89 (ddd, 1H), 1.71 (ddt, 1H), 1.58 (m, 1H), 1.23 (m, 1H), 1.15 (dt, 1H), 1.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2 (HC═), 131.6 (HC═), 78.5 (HCO), 56.1 (H_3CO), 33.5 (H_2C), 33.2 (HC), 29.8 (HC), 25.8 (H_2C), 17.5 (H_2C). 5-*endo*-Methoxybicyclo[2.2.2]oct-2-ene (**2b**): ^1H NMR (500 MHz, $CDCl_3$) δ 6.36 (t, 1H), 6.09 (t, 1H), 3.49 (m, 1H), 3.26 (s, 3H), 2.84 (br s, 1H), 2.54 (br s, 1H), 1.84 (ddd, 1H), 1.34 (m, 2H), 1.28 (m, 1H), 1.16 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2 (HC═), 130.0 (HC═), 80.1 (HCO), 55.5 (H_3CO), 35.7 (H_2C), 33.4 (HC), 29.8 (HC), 24.3 (H_2C), 22.0 (H_2C).

7-Methoxybicyclo[3.2.0]hept-2-enes (7). To a solution of 6.0 mL (0.19 mol) of anhydrous hydrazine in 15 mL of absolute ethanol was added 3.4 g (0.025 mol) of 7-methoxybicyclo[3.2.0]hept-2-en-6-one[14] dissolved in 6 mL of absolute ethanol. After the reaction mixture was heated overnight at 60 °C, the reaction mixture was poured into 40 mL of water and worked up in a fashion analogous to that employed for preparing **4** to afford the crude hydrazone (2.60 g, 70%). IR (cm^{-1}) 3340 (m), 3280 (w), 3025 (w), 1615 (m), 1090 (s), 720 (s). The low-temperature Wolff−Kishner reduction to prepare **7** was then accomplished using conditions similar to those employed for the synthesis of compound **1**. Conversion of 2.53 g of 7-methoxybicyclo[3.2.0]hept-2-en-6-one hydrazone to **7** was accomplished in 28% yield. Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 76.70; H, 9.78. MS (*m*/*z*) 124 (2%), 66 (100%). Separation of epimers **7a** and **7b** from a mixture that was 9:91 **7a**:**7b** by GC analysis was achieved using preparative GC. 7-*exo*-Methoxybicyclo[3.2.0]hept-2-ene (**7a**): ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (m, 1H), 5.70 (m, 1H), 3.56 (ddd, 1H), 3.25 (s, 3H), 3.18 (m, 1H), 2.91 (m, 1H), 2.57 (qq, 1H), 2.16 (m, 2H), 1.88 (pent, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.1 (HC═), 130.5 (HC═), 82.4 (HCO), 55.4 (H_3CO), 53.0 (HC), 40.3 (H_2C), 34.4 (H_2C), 31.6 (HC). 7-*endo*-Methoxybicyclo[3.2.0]hept-2-ene (**7b**): ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5. 75 (m, 1H), 3.98 (dd, 1H), 3.54 (m, 1H), 3.22 (s, 3H), 2.45 (m, 3H), 2.14 (dq, 1H), 1.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.1 (HC═), 129.2 (HC═), 75.8 (HCO), 55.6 (H_3CO), 52.6 (HC), 40.4 (H_2C), 35.2 (H_2C), 27.7 (HC).

5-Methoxybicyclo[2.2.1]hept-2-enes (8). A sample of 1.7 g (0.073 mol) of sodium hydride (2.9 g of a 60% dispersion in mineral oil, which was removed by rinsing with pentane) was suspended in 20 mL of anhydrous THF under nitrogen. A solution of 6.0 g (0.055 mol) of 5-norbornen-2-ol in 10 mL of THF was then added

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dropwise to the suspension. After 2 h, 15 mL (34. g, 0.24 mol) of methyl iodide was added to the reaction mixture, which was stirred overnight. Workup as in the synthesis of **2** gave **8** (6.1 g, 90%), which consisted of a 19:81 mixture of **8a**:**8b**, respectively, as determined by GC analysis. Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.58; H, 9.92. MS (*m*/*z*) 124 (6%), 66 (100%). IR (cm^{-1}) 3060 (w), 1090 (s), 660 (s). Separation of epimers **8a** and **8b** from the 19:81 mixture of **8a**:**8b** was achieved using preparative GC. The ^{1}H NMR and ^{13}C NMR spectral data for **8a** are in accord with chemical shifts reported in the literature.[37] 5-*exo*-Methoxybicyclo[2.2.1]hept-2-ene (**8a**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (dd, 1H), 5.89 (dd, 1H), 3.35 (m, 1H), 3.31 (s, 3H), 2.88 (br s, 1H), 2.77 (br s, 1H), 1.55 (m, 3H), 1.29 (dt, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7 (HC═), 133.2 (HC═), 82.1 (HCO), 56.8 (H_3CO), 45.9 (HC), 45.8 (H_2C), 40.4 (HC), 34.2 (H_2C). 5-*endo*-Methoxybicyclo[2.2.1]hept-2-ene (**8b**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (dd, 1H), 5.97 (dd, 1H), 4.03 (dt, 1H), 3.26 (s, 3H), 3.09 (br s, 1H), 2.77 (br s, 1H), 1.94 (m, 1H), 1.42 (m, 1H), 1.21 (d, 1H), 0.85 (dt, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0 (HC═), 131.2 (HC═), 81.7 (HCO), 56.7 (H_3CO), 47.3 (H_2C), 45.0 (HC), 42.2 (HC), 34.0 (H_2C).

Gas-Phase Reactions. Thermal reactions were conducted in an apparatus previously described.[11] Thermolysis samples were analyzed by GC on an HP cross-linked methyl silicone column (50 m × 0.2 mm i.d. × 0.10 μm film thickness) operating at an initial temperature of 60 °C held for 1 min followed by a temperature ramp of 3.0 °C/min for **1a** and **1b** (1.5 °C/min for **7a** and **7b**) to a maximum temperature of 120 °C. Retention times (min) were as follows: **2a** (13.6), **2b** (14.4), **1a** (14.7), **1b** (15.6), and the internal standard undecane (16.4) as in Figure 1 (Supporting Information); **8a** (10.2), **8b** (10.7), **7a** (11.5), **7b** (12.0), and the internal standard 4-methylnonane (13.2). Concentrations of fragments 1,3-cyclohexadiene (or 1,3-cyclopentadiene) and methoxyethene were determined by difference as compared to a time zero sample for each kinetic run.

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Supporting Information Available: NMR spectra for **1a**, **1b**, **2a**, **2b**, **3a**, **3b**, **6a**, **6b**, **7a**, **7b**, **8a**, and **8b**; tables of mole fractions for thermal runs of **1a** and **1b** at 250, 275, and 300 °C; copies of first-order kinetic rate and Arrhenius plots for **1a** and **1b**; a representative GC chromatogram for the thermal reactions of **1a** and **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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