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A vinylcyclobutane substrate designed as a cyclopropylcarbinyl radical probe†

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Phyllis A. Leber,* Ryan M. Bell, Carlton W. Christie and Joseph A. Mohrbacher III

Appending a spirocyclopropane linkage to bicyclo[3.2.0]hept-2-ene is achieved by selective kinetic cyclopropanation of 6-methylenebicyclo[3.2.0]hept-2-ene. The resultant vinylcyclobutane undergoes [1,3] migration as the dominant thermal process. A minor cyclopropylcarbinyl (CPC) rearrangement product clearly implicates a diradical transition structure. The presence and absence of other potential thermal products have enabled us to construct a detailed mechanistic proposal to account for all viable dynamic processes.

Vinylcyclobutanes undergo ring expansion to cyclohexenes *via* formal [1,3] sigmatropic carbon migrations. A vibrant mechanistic debate ensued virtually since the discovery of this reaction type 50 years ago.[1] Frey initially proposed a self-consistent mechanistic analysis—a stepwise process involving singlet diradical intermediates[2]—to account for the results of this thermal reaction. Yet Woodward and Hoffmann, in their treatise on the *Conservation of Orbital Symmetry*, asserted that the dramatic stereospecificity observed in a seminal experiment was consistent with a concerted mechanism.[3]

Of the two criteria of concert, energetics and stereochemistry, explicated by Gajewski,[4] vinylcyclobutane-to-cyclohexene rearrangements have never satisfied the energetic criterion due to their relatively high activation energies. Therefore, an experimental focus on the stereochemical criterion of concert has led over time to the recognition that the degree of stereoselectivity in [1,3] carbon shifts is highly dependent on the conformational flexibility of a given substrate ground state and that of its corresponding transition structure.[5] As more experimental evidence of negligible stereoselectivity has been compiled, the view that thermal activation of vinylcyclobutanes affords short-lived nonstatistical diradical transition structures has gained prominence in the past decade.[6,7]

Department of Chemistry, Franklin & Marshall College, Lancaster, PA, USA. E-mail: phyllis.leber@fandm.edu

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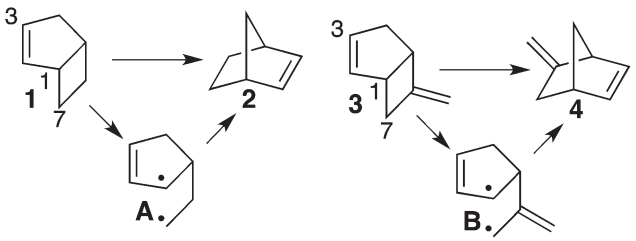


Fig. 1 Thermal isomerizations of **1** and **3**.

Bicyclo[3.2.0]hept-2-ene (**1**) undergoes thermal isomerization[8] to bicyclo[2.2.1]hept-2-ene (**2**), Fig. 1. This conversion has received considerable attention as an exemplar of a [1,3] sigmatropic rearrangement.[3,6] Competitive isomerization and fragmentation processes at temperatures in excess of 300 °C convert **1** either to its isomer norbornene (**2**) or to fragments cyclopentadiene and ethylene, which can form directly from **1** or indirectly *via* Diels–Alder cycloreversion of **2**. Hasselmann has studied the thermal chemistry of the related hydrocarbon 6-methylenebicyclo[3.2.0]hept-2-ene (**3**) and has reported that **3** is converted exclusively to its isomer 5-methylenebicyclo [2.2.1]hept-2-ene (**4**) at temperatures of 186–218 °C.[9] For comparative purposes rate constants can be computed at 275 °C, a temperature that has been used as a benchmark for other bicyclo[3.2.0]hept-2-enes, based on the reported activation parameters for each thermal process (Table 1).

The relative rate enhancement of almost three orders of magnitude for **3** compared to **1** (Table 1) is a reflection of the differences in reported activation energies for the respective thermal reactions of **1** and **3**, a value consistent with that attributed to allylic resonance energy. Given the difference in the magnitude of the energy barriers of **1** and **3**, a diradical process is a plausible mechanistic proposal. Structural representations for the diradical intermediates **A** and **B** formed from compounds **1** and **3** by homolytic cleavage of their respective C1–C7 bonds show that both **A** and **B** are 1,4-diradicals. Dynamic simulations of the isomerizations of **1** and **3** support the intermediacy of 1,4-diradicals **A** and **B** that exist

Table 1 Relative rates of **1** and **3**

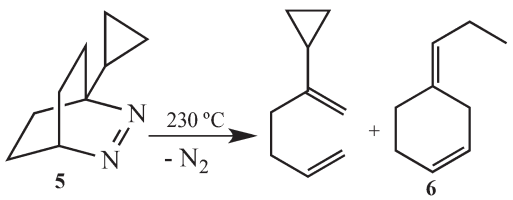
Cmpd.	k_d (275 °C)	k_{rel}	E_a (kcal mol^{-1})	Ref.
1	9.2×10^{-6} s^{-1}	1	49.6	8
3	7.9×10^{-3} s^{-1}	860	39.6	9

on shallow potential energy surfaces.[10,11] Thus, the preponderance of scientific evidence now supports 1,4-diradical transition structures to account for the [1,3] sigmatropic rearrangements of compounds **1** and **3**.[6]

The cyclopropyl carbinyl-to-homoallylic radical rearrangement (eqn (1)) has been used to monitor kinetics, to elucidate mechanisms, and to detect free radicals in biochemical[12] and chemical[13] reactions. Numerous examples exist where CPC rearrangements have been utilized as probes of 1,4-diradical intermediates generated under photolytic conditions in Norrish Type II photoreactions,[14] [2 + 2] photocycloadditions,[15] and diazo cycloreversions.[16] Two general outcomes occur subsequent to the CPC rearrangement in triplet diradical intermediates: H-atom transfer and/or diradical recombination/cyclization.

(1)

Yet there is a virtual dearth of reports of CPC involvement in singlet 1,4-diradicals. Engel *et al.* observed that cyclopropyl substituents at C1 and/or C4 of 2,3-diazabicyclo[2.2.2]oct-2-ene (DBO) resulted in enhanced photoreactivity, but not thermal reactivity. Although they report 2-cyclopropyl-1,5-hexadiene as the major product in the thermolysis of 1-cyclopropyl-DBO (**5**) at 230 °C, the H-atom transfer product **6** represents 2% of the product mixture (eqn (2)).[17]



(2)

We have thus conceived of spiro[bicyclo[3.2.0]hept-2-ene-6,1′-cyclopropane] (**7**) as a potential probe of a singlet 1,4-diradical generated under thermal conditions. Based on the reported literature precedent, we anticipated that any CPC rearrangement products would constitute minor components of the product mixture. As a consequence, we expected the major thermal process to be [1,3] sigmatropic rearrangement of **7** to spiro[bicyclo[2.2.1]hept-5-ene-2,1′-cyclopropane] (**8**), a known compound.[16,18]

All feasible CPC rearrangement products due to cyclization or hydrogen transfer processes are shown in Fig. 2. If compound **7** were indeed a suitable substrate for a CPC rearrangement, secondary diradical **C** could be produced from primary diradical **D**. Such a CPC diradical **C** might yield cyclization

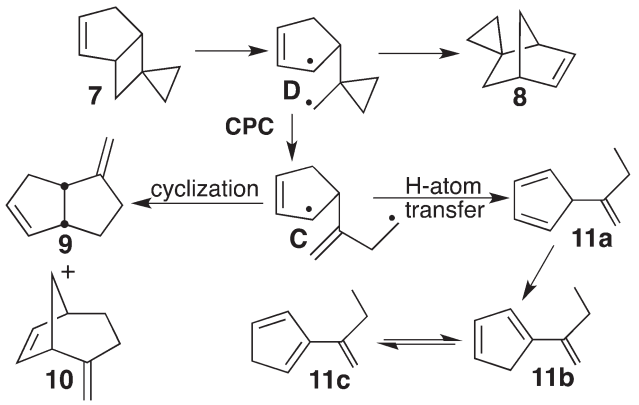


Fig. 2 Potential thermal reactions of **7**.

products **9** and **10** and/or H-atom transfer products **11b** and **11c** *via* the intermediacy of **11a**.

The novel synthetic strategy we employed for the preparation of both **7** and **8** was to attempt a selective kinetic cyclopropanation of the exocyclic olefin of **3** (or **4**) to yield **7** (or **8**). We reasoned we could exploit a modest reactivity difference between the methylenecyclobutane and cyclopentene olefins in diolefin **3**. Although we could not necessarily assume a similar reactivity differential for the two olefins in **4**, we noted that Zefirov[18] had achieved a high degree of selectivity for dichlorocarbene addition to the exocyclic olefin in **4** under phase-transfer conditions but had observed preferential addition of methylene to the endocyclic olefin upon treatment of **4** with diazomethane at −10 °C. To avoid the use of diazomethane as a means of delivering methylene, we envisioned the Furukawa modification[19] of the Simmons–Smith Reaction as a viable methodology for sequential addition of reagents, including the homogenous catalyst diethylzinc, at reduced temperatures. We were able to achieve reasonable selectivity by holding the reaction temperature between 0 and −5 °C.

The structures of all potential CPC rearrangement products were proven by independent synthesis. Wittig methylenation of known ketones bicyclo[3.3.0]oct-6-en-2-one[20] and bicyclo[3.2.1]oct-6-en-2-one[21] afforded compounds **9** and **10**, respectively. Base-catalyzed isomerization of 6-ethyl-6-methylfulvene, which was prepared by treatment of cyclopentadienyl anion with butanone,[22] resulted in a mixture of **11b** and **11c**.[23]

A series of ten thermal reactions of compound **7** were obtained at 275 °C for various times between 1 and 36 h, or 9 half-lives. Isomer **8**, which converged toward a maximum value of 82 mole%, is indeed the dominant product. Product **8**, a spironorbornene, does not fragment but is stable under the thermal reaction conditions, an observation we attribute to the high energy barrier for the Diels–Alder cycloreversion to cyclopentadiene and methylenecyclopropane, which possesses an estimated 41–43 kcal mol^{-1} of strain energy.[24] Based on the results of a DFT computational study of the Diels–Alder reaction of cyclopentadiene and methylenecyclopropane, a prohibitive $\Delta G^{\neq}$ value of 52.6 kcal mol^{-1} has been estimated for cycloreversion.[25]

An experimental concentration *versus* time kinetic plot for disappearance of compound **7** gave a first-order rate constant for decomposition (k_d) of **7** at 275 °C of 4.7×10^{-5} s^{-1}. While compound **7** reacts significantly slower than does compound **3**, it is ten times more reactive than **1** based on the rate constant measured directly at 275 °C.[8] This observed rate enhancement might thus promote a CPC rearrangement of diradical **D** to diradical **C** (Fig. 2), as previously surmised. A set of minor isomeric products present in the thermal reaction mixture reached a maximum value in excess of 7 mole% at 12 h. Compound **9** accounted for 2–3 mole% of the total product mixture.[26] The presence of compound **9** in the thermal reaction mixture constitutes indirect evidence of diradical **C** and, by implication, **D**.

Compound **10**, another potential CPC cyclization product, was conspicuously absent from the thermal reaction of **7**. Two product isomers with GC retention times of 12.2 and 12.5 min were initially assumed to correspond to compounds **11b** and **11c** (Fig. 2). These peaks were ultimately assigned to compounds **12b** and **12c**, which can be accessed directly from diradical conformer $\mathbf{D_1}$ (Fig. 3) by an H-atom transfer. Synthesis of an isomeric mixture of **12b** and **12c** was accomplished by treating 1-bromo-1-methylcyclopropane sequentially with *t*-butyl lithium and then 2-cyclopentenone at low temperature using an adaptation of a procedure devised for a related compound.[27]

Two exit channels, [1,3] carbon shift to **8** and H-atom transfer to **12b** and **12c**, constitute a total of 87% of the product mixture (Fig. 3). As C1–C7 bond cleavage begins, compound **7** like **1** preferentially adopts an *endo* transition structure, which according to Carpenter is stabilized by residual bonding between C1 and C7.[10] What differs however is that the primary alkyl radical center at C7 in some $\mathbf{D_1}$ transition structures slides past C3 to permit abstraction of the *endo*-H atom at C4, thus giving rise to products **12b** and **12c** (Fig. 3).

In the less favorable case where compound **7** assumes an *exo* trajectory during C1–C7 bond cleavage, diradical **D** conformers $\mathbf{D_2}$ and $\mathbf{D_3}$ can interconvert by rotation about the C5–C6 bond. As the primary radical center at C7 foregoes optimal diradical stabilization, fragmentation to cyclopentadiene and methylenecyclopropane can proceed from the $\mathbf{D_2}$ conformer. A continuation of rotation about the C5–C6 bond yields conformer $\mathbf{D_3}$, which can undergo CPC rearrangement to homoallylic diradical transition structure $\mathbf{C_1}$ that immediately collapses to CPC product **9**.

The ability of diradical **C**, compared to diradical **D**, to explore conformational space is much more limited. Once formed, $\mathbf{C_1}$ like $\mathbf{D_1}$ should in principle be able to access an *endo* trajectory. Yet neither the potential CPC rearrangement product **10** nor the isomeric mixture **11b** and **11c** is observed. We attribute the absence of these products to a short lifetime for diradical $\mathbf{C_1}$ and/or insufficient angular momentum once C5–C6 bond rotation commences.

The 10-fold rate enhancement of **7** compared to **1** is intriguing because both vinylcyclobutanes would afford primary alkyl, allyl diradical transition structures. What constitutes experimental evidence for a C6-cyclopropyl substituent effect can be accounted for either by electronic stabilization of the primary radical center at C7 in singlet diradical **D** or by relief of ring strain due to the C6 spiro linkage. According to de Meijere,[28] spiro[2.2]pentane possesses remarkable thermal stability despite a calculated value reported by Lammertsma[29]

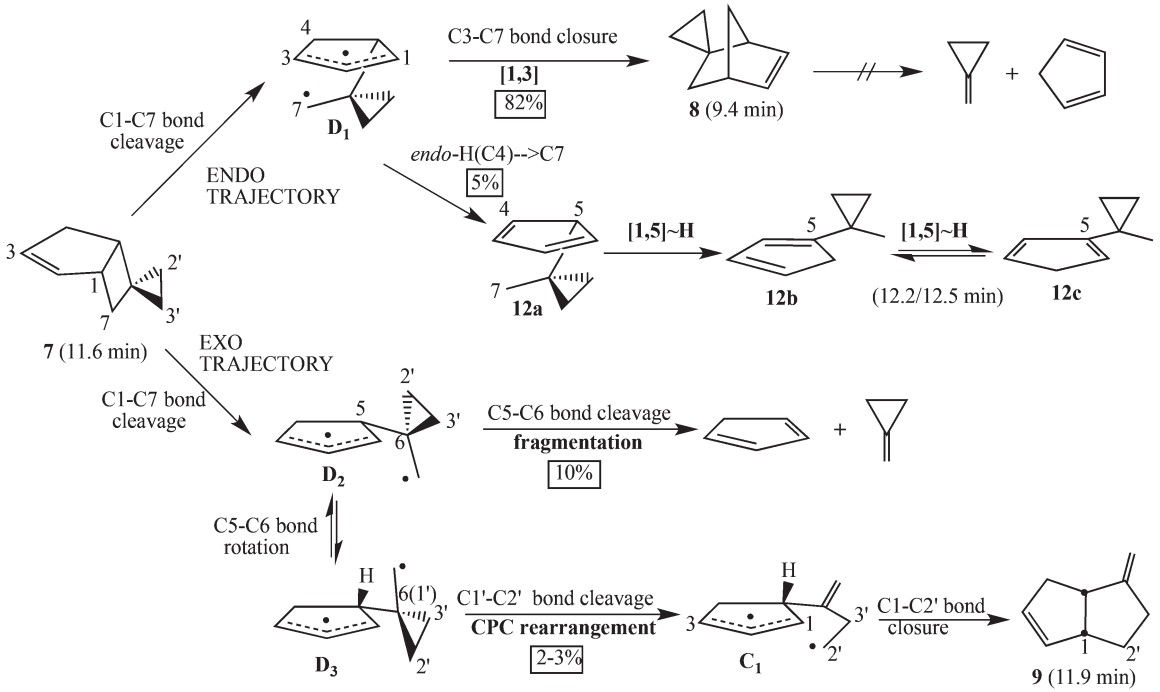


Fig. 3 Thermal exit channels observed for **7**.

of 8.1 kcal mol^{-1} for ΔSE, defined as the difference between the strain energy of the spiro compound and the sum of the strain energies of the separate rings. In contrast, spiro[2.3]-hexane, with an estimated value of ΔSE = 1.3 kcal mol^{-1},[29] would appear to experience relatively little ring strain. While these values do not preclude a potential ring strain contribution to the observed rate effect, we surmise that cyclopropyl hyperconjugation exerts a more pronounced rate effect. This analysis is supported by prior research on azoalkane decomposition reactions[30] by Martin and Timberlake, who concluded a rate enhancement by a cyclopropyl substituent attached to an incipient radical center can be explained by "a postulated stabilization of product radicals by cyclopropyl conjugation." A reported value of 3 kcal mol^{-1} of corresponding stabilization in the cyclopropylcarbinyl radical[31] can account for most if not all of the rate effect.

In summary, selective kinetic cyclopropanation converts **3** to **7**. A thermal study of **7** has provided definitive experimental evidence for 1,4-diradical intermediate **D** by an observed rate enhancement and for CPC diradical intermediate **C** due to product **9** formation. We intend to examine vinylcyclobutanes related to **7** for further evidence of CPC rearrangements. In particular, we believe that the bicyclo[4.2.0] analog of compound **7** is a suitable substrate to test our earlier prediction that 1,4-diradicals derived from bicyclo[4.2.0]oct-2-enes are less tightly associated[5] than those derived from bicyclo[3.2.0]-hept-2-enes. If so, they might well be more prone to CPC rearrangements.

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